Stem cell transplantation in multiple myeloma and other plasma cell disorders (report from an EBMT preceptorship meeting)

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Abstract

The European Society for Blood and Marrow Transplantation Chronic Malignancies Working Party held a preceptorship meeting in Turin, Italy on 25–26 September 2014, to discuss the role of stem cell transplantation (SCT) in the treatment of multiple myeloma and other plasma cell disorders. Scientists and clinicians working in the field gathered to discuss a variety of topics including the results of recent clinical trials, basic research, the concept of minimal residual disease, and immune modulation. As individual presentations revealed, important advances have occurred in our understanding of the pathophysiology of myeloma and the role that SCT, along with other forms of immunotherapy, plays in treating it. Each presentation stimulated discussion and exchange of ideas among the attendants. We decided to summarize and, importantly, to update the meeting proceedings in this review to share stimulating discussions and ideas on potentially novel treatment strategies among clinicians.

Keywords

- Multiple myeloma,
- new drugs,
- stem cell transplantation

Introduction

Multiple myeloma (MM) is the prototype of plasma cell disorders and is characterized by malignant plasma cell proliferation, cytopenias, renal insufficiency, and bone destruction. Median age at diagnosis is around 70 years. Asymptomatic (smoldering) MM is managed with a watch and wait approach [1] and therapy is only initiated on progression to symptomatic disease. The modern therapeutic armamentarium includes combinations of proteasome inhibitors (bortezomib or carfilzomib), immunomodulatory drugs (IMiDs) (thalidomide, lenalidomide, or pomalidomide), steroids, alkylating agents, or anthracyclines. Various monoclonal antibodies are under evaluation in clinical trials. Elotuzumab is an antibody targeting signaling lymphocytic activation molecule F7 while daratumumab and SAR650984 are directed against the plasma cell surface antigen CD38.
Several predictors of disease progression have been identified, such as beta-2 microglobulin, albumin, plasma cell labeling index, lactate dehydrogenase, and cytogenetics.[2] However, whereas it is possible to stratify MM by risk at diagnosis, individualized therapies for various risk groups have not yet been designed. Moreover, the therapeutic algorithm should also depend on patient performance status and comorbidities. Toxicity is not necessarily associated with patient age, though older patients tend to be less fit.[3]

Important advances have occurred in our understanding of the pathophysiology of MM and the role that stem cell transplantation (SCT) plays in its treatment. Frontline autologous SCT (auto-SCT) is considered the standard of care for all eligible patients.[4] Recent evidence has confirmed its superiority compared with other non-SCT approaches, even after the introduction of novel agents in induction schemas.[5] Conversely, data on allogeneic SCT (allo-SCT) in MM are not consistent among different institutions.[6,7] This review is focused on the current roles of SCT procedures in MM and other plasma cell disorders and on the future potential role of immunotherapy strategies.

Autologous stem cell transplantation

The long-term survival of MM patients has dramatically increased in the last 20 years, particularly for younger patients. This is most likely attributable to the introduction and development of auto-SCT. Conversely, survival of older patients and of those who are not eligible for intensive regimens remains poor.[8] The first results of conventional chemotherapy versus high-dose chemotherapy (HDC) and auto-SCT were published by the Intergroupe Francophone du Myélome (IFM) in 1996. Two hundred newly diagnosed patients younger than 65 years old were randomized in two arms. The 5-year estimates of overall survival (OS) were 52% and 12% in auto-SCT and conventional chemotherapy arm, respectively ($p = 0.03$).[4] A second large prospective study by the UK Medical Research Council (MRC) addressed the same question in 407 patients. Results substantially confirmed the superiority of frontline HDC and auto-SCT as compared with conventional chemotherapy. The gain in median OS was in the order of 1 year.[9] By contrast, other randomized trials failed to show OS or progression-free survival (PFS) advantages. Attal et al. reported a systematic review and meta-analysis of studies comparing upfront HDC and auto-SCT versus chemotherapy alone. Results indicated a benefit in terms of PFS for HDC and auto-SCT, although this

advantage did not translate into longer OS. Of note, the nine studies analyzed did not include novel agents in the treatment plan.[10]

Palumbo et al. recently reported results of a prospective comparison of HDC with auto-SCT versus melphalan-prednisone-lenalidomide (MPR). Two hundred and seventy-three patients younger than 65 years were randomized in the two arms. After a median follow-up of 51.2 months, high-dose melphalan (MEL) and auto-SCT significantly improved both PFS and OS, compared with MPR. Median PFS of auto-SCT patients was 43 months compared with 22.4 months in the MPR arm ($p < 0.001$). The 4-year estimates of OS were 81.6% and 65.3% for auto-SCT and MPR arm, respectively ($p = 0.02$) [5] [Figure 1].

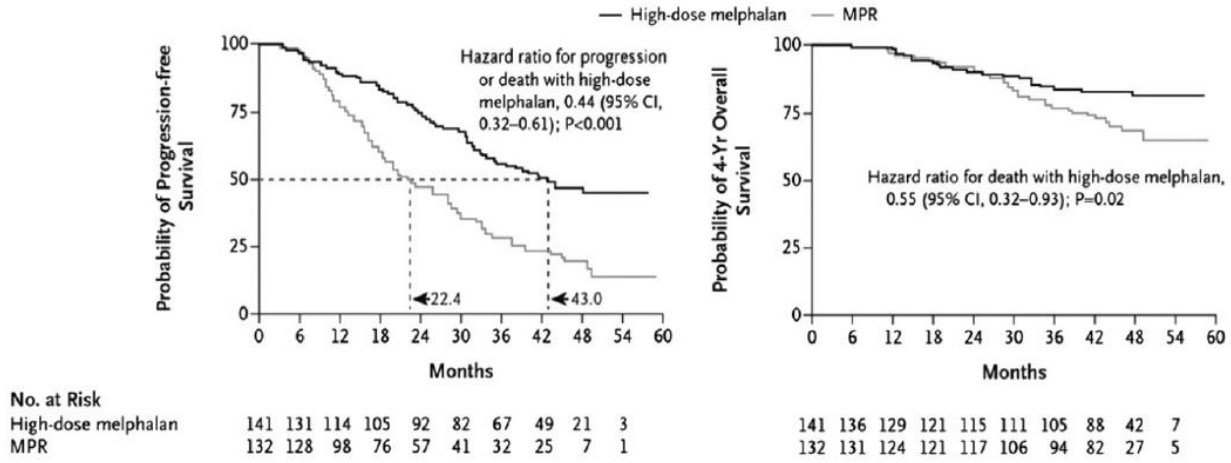

Figure 1. Progression-free and overall survival from the start of consolidation treatment in 273 patients. Patients who completed induction and mobilization were randomized to high-dose melphalan and auto-SCT or to consolidation with melphalan-prednisone-lenalidomide (MPR), followed by lenalidomide maintenance.[5] (Figure adapted from Palumbo et al.).

Though HDC and auto-SCT are regarded as the standard of care for eligible MM patients, the optimal timing of auto-SCT remains unclear. Two phase III trials are currently in progress to address this issue: the European Myeloma Network (EMN-02/HO95) trial (NCT01208766) and the IFM/Dana-Farber Cancer Institute 2009 trial (NCT01208662) are designed to evaluate early versus late auto-SCT. Results are not yet available. The most commonly used conditioning regimen is MEL at 200 mg/m^2 (MEL 200), which has replaced total body irradiation. Other regimens are being evaluated in phase II trials, including bortezomib-MEL, radiotherapy-based regimens (e.g. total marrow irradiation, anti-CD38 radio-immunotherapy, Holmium [^{166}Ho]), as well as alternative chemotherapies (e.g. bendamustine, treosulfan, thiotepa). The combination of busulfan-MEL at 140 mg/m^2 (MEL 140) provided improved PFS, but increased non-relapse mortality (NRM) due to veno-occlusive disease when compared to MEL 200.[11]

Stem cell collection

The stem cell harvesting process in MM is hampered by a collection failure rate between 5% and 10%. Musto et al. recently evaluated 1348 patients enrolled in five Italian trials that included novel agents in the treatment plan. Stem cell mobilization regimen was invariably cyclophosphamide and granulocyte colony-stimulating factor. The authors defined collections as unsuccessful or sub-optimal if the CD34 + cell count in

the harvest was below 2×10^6/kg/recipient body weight or 5×10^6/kg, respectively. A sub-optimal collection occurred in 12.4% of patients, whereas collection was unsuccessful in 8.4%. Factors associated with poor mobilization were age and hematological toxicity during prior induction.[12] Novel strategies for optimizing stem cell collection includes the addition of the alpha chemokine receptor CXCR4 antagonist plerixafor in selected patients. Lemoli et al. reported a prospective study on the use of plerixafor in 83 MM patients who were poor mobilizers. Patients were classified as predicted or proven poor mobilizers accordingly to the Gruppo Italiano Trapianto di Midollo Osseo criteria.[13] Harvests were successful in more than 80% regardless of treatment history.[14] Interestingly, platelet count below 100 000/mm^3 was associated with poor mobilization in a multivariate model.

Post auto-SCT consolidation and maintenance

Treatment options for consolidation currently include second auto-SCT, bortezomib, or lenalidomide as single agents or in combination, and bisphosphonates. Investigators at various institutions evaluated the potential benefit of a second auto-SCT consolidation. Kumar et al. performed a meta-analysis on available data.[15] Although tandem auto-SCT was associated with better response rates, the result was overshadowed by significantly higher toxicity (risk ratio for NRM = 1.71, 95% CI = 1.05–2.79). There was no OS benefit. Therefore, upfront tandem auto-SCT is still controversial. Another approach that may delay relapses is maintenance. Substantially all the novel agents have been tested. Thalidomide, bortezomib, and lenalidomide are used most commonly in clinical trials, usually combined with steroids. In a meta-analysis, thalidomide appeared to provide OS benefit, but it was associated with severe side effects, particularly deep vein thrombosis and peripheral neuropathy.[16] Randomized studies have shown a benefit for lenalidomide maintenance in terms of PFS.[5,17,18] Palumbo et al. reported results of 251 patients randomized between lenalidomide maintenance therapy and no maintenance therapy. The median PFS was significantly longer with lenalidomide maintenance (41.9 months versus 21.6 months; $p < 0.001$). The benefit did not translate into longer 3-year OS. The most frequent grade 3–4 adverse event was neutropenia, which occurred in 23.3% of patients who received lenalidomide maintenance. Importantly, 11 patients (2.8%) in the lenalidomide maintenance arm developed a secondary malignancy (lung, breast, or prostate cancer). The authors concluded that longer follow-up is needed to evaluate the benefit of prolonged maintenance.[5] The theoretical risk of chemo-resistance after lenalidomide maintenance failure must be assessed. Patients should be informed about the risk of secondary neoplasm with long-term administration of lenalidomide. However, we think that lenalidomide maintenance should be considered, especially in patients with a predicted high risk of early relapse. In the MRC study of bisphosphonate (clodronate) maintenance versus placebo published in 2001, median OS in the clodronate arm was 59 months, versus 37 months for placebo (p=0.004). The benefit was significant only in the subgroup of 153 patients presenting without vertebral fractures.[19] In another MRC trial (Myeloma IX), the benefit was larger with zoledronic acid than with clodronate (HR= 0.85; p = 0.0178), even after adjustment for previous skeletal events.[20]

The phase III StAMINA trial (BMT-CTN 0702) has completed the enrollment. Fifty-four United States centers participated. Patients were randomized in three arms: tandem auto-SCT with lenalidomide maintenance; single auto-SCT with RVD consolidation and lenalidomide maintenance; single auto-SCT with upfront lenalidomide maintenance. The results will probably help to clarify the impact of HDC consolidation and lenalidomide maintenance in MM.

Treatment of post auto-SCT relapse

No standard therapy is available for relapses occurring after auto-SCT. Clinicians should consider disease characteristics, patient medical history, and previous treatments. The high-risk disease is characterized by short response duration, cytopenias, renal failure, advanced bone lesions, extra-medullary disease, and adverse cytogenetics. Important patient characteristics include performance status, age, and comorbidities. Regarding treatment history, the various drugs used alone or in combination should be reviewed. The quality of response achieved and, importantly, the eventual toxicities should be considered. Moreover, clinicians should involve patients in the treatment selection process. General strategies for relapse management are non-SCT approaches, auto-SCT salvage, and allogeneic (allo)-SCT. Non-SCT approaches should include novel agents alone or in combination. Chemotherapy can also be used. The European Society for Blood and Marrow Transplantation (EBMT) conducted a randomized trial comparing bortezomib-thalidomide-dexamethasone (VTD), $n = 135$ to thalidomide-dexamethasone (TD), $n = 134$. Time to progression (TTP) and PFS were both significantly improved in the VTD arm (19 versus 13 months, and 18 versus 13 months, both p values = 0.001). The 2-year estimate of OS was similar in the two groups (71% versus 65%, $p = 0.093$). This trial showed the superiority of a triple combination versus a dual combination in terms of PFS. The benefit may be due to a more rapid and deeper response level overcoming the potential resistance. The synergistic combination effect of targeted agents would not occur if drugs were given sequentially. However, VTD was associated with a higher incidence of grade 3 neurotoxicity.[21]
Other novel agents have been evaluated in relapsed patients.[22] Combinations including the anti-CS1 elotuzumab and the anti-CD38 daratumumab had the most promising results. These agents have been tested mainly in combination with lenalidomide or bortezomib plus steroids. In a small phase II trial, elotuzumab, lenalidomide, and dexamethasone provided an encouraging 82% partial response (PR) rate in relapsed MM patients. After a median follow-up of 16.4 months, the median TTP was not reached. Of note, two of 28 treated patients experienced grade 3–4 allergic reactions during elotuzumab first cycle.[23] Those preliminary data supported a randomized phase III trial, which was recently completed. Six hundred and forty-six patients from 168 sites were randomly assigned to receive either elotuzumab, lenalidomide, and dexamethasone, or lenalidomide and dexamethasone. Median PFS in the triple combination arm was 19.4 months versus 14.9 months in the control group, for an HR of 0.70 ($p < 0.001$). The data were not mature enough to evaluate whether the benefit translated into significantly longer OS.[24]

A number of studies evaluated the outcome of second auto-SCT as salvage therapy after disease progression. The predictor historically associated with worse TTP after salvage auto-SCT is the response duration after the first auto-SCT.[25] Alvares et al. confirmed this finding in 83 patients treated with a salvage second auto-SCT. Twenty patients had relapsed within 18 months from the first auto-SCT. The remaining 63 patients had experienced longer remission. Patients with a PFS <18 months had median OS from second auto-SCT of less than 6 months; conversely, patients with longer PFS had an OS from second auto-SCT approaching 3 years ($p < 0.001$).[26] In the National Cancer Research Institute Myeloma X study, patients who relapsed after at least 18 months from auto-SCT were randomized to MEL 200 and auto-SCT ($n = 89$) or weekly cyclophosphamide ($n = 85$) for 12 weeks. Before randomization, all patients received a bortezomib-based re-induction treatment. Median TTP by intention to treat analysis was 19 months in the auto-SCT arm, compared to 11 months in the chemotherapy arm (HR: 0.36 [95% CI: 0.25–0.53; $p < 0.0001$]). This study provides evidence for the improved efficacy of second auto-SCT when compared with cyclophosphamide in patients eligible for intensive therapy.[27] Whether auto-SCT salvage is superior to non-SCT approaches incorporating new drugs is an open question.

The best results with allo-SCT in MM are obtained when the procedure is applied early in the disease course. However, allo-SCT salvage constitutes a third option for patients with chemosensitive relapse. Kröger et al. prospectively investigated the role of unrelated donor, reduced-intensity conditioning (RIC)

allo-SCT in 49 patients relapsing after auto-SCT. PFS and OS were 10 and 22 months, respectively. Cumulative incidence of NRM at 1 year was 25%. The presence of human leukocyte antigen (HLA) mismatches was associated with worse OS (HR: 2.97; 95% CI: 1.42–6.21) and PFS (HR: 2.25; 95% CI: 1.16–4.35) in univariate analysis.[28] Several other retrospective studies reported non-conclusive results.[29,30]

In summary, various, non-standard therapies are available for post-auto-SCT failures. When possible, patients should be considered for prospective clinical trials. Non-SCT approaches should be conducted with a double or a triple combination that includes novel agents. Second auto-SCT seems to provide the best results in patients with a first remission lasting longer than 18 months. Allo-SCT should be performed in the setting of clinical trials.

Autologous stem cell transplantation in elderly patients

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As discussed earlier, HDC followed by auto-SCT consolidation is considered standard of care in patients with MM. However, the treatment is associated with significant toxicity that limits its use in elderly patients and patients with comorbidities. We reviewed data on auto-SCT in elderly patients. One of the first prospective trials on auto-SCT in patients between 50 and 70 years was published in 2004 by an Italian group.[31] At diagnosis, 194 patients were randomly assigned to receive either six courses of MEL and prednisone (MP) or two courses of dexamethasone-doxorubicin-vincristine debulking followed by two courses of MEL 100 mg/m^2 (MEL 100) plus auto-SCT. The 3-year estimates of OS were 62% versus 77% ($p < 0.001$) in the non-SCT and the SCT arm, respectively. Similar results were observed when the analysis was restricted to patients aged 65–70 years. In this subgroup, MEL 100 auto-SCT increased OS from 58% to 73% ($p = 0.01$). The superiority of reduced intensity auto-SCT to conventional-dose chemotherapy was not confirmed by the IFM 99-06 trial. In this study, 447 previously untreated MM patients older than 65 years were randomized to receive either MP ($n = 196$), MP and thalidomide (MPT; $n = 125$), or two debulking courses of vincristine (continue infusion), doxorubicin, and dexamethasone followed by a tandem MEL 100 auto-SCT ($n = 126$). After a median follow-up of 51.5 months, median OS was 33.2 months, 51.6 months, and 38.3 months for MP, MPT, and MEL 100 auto-SCT, respectively. Auto-SCT was not superior to MP and was associated with inferior outcomes compared to MPT.[32] However, a number of retrospective single-center studies have indicated that auto-SCT may be safe and effective for selected elderly patients.[3,33–38] The EBMT in Europe and the Center for International Blood and Marrow Research (CIBMTR) in Northern America recently reported two large registry studies. The EBMT analyzed data of 53 675 patients

transplanted between 1991 and 2010. Patients were divided into six age categories (<40, 40–49, 50–59, 60–64, 65–69, and ≥70 years). Data were grouped in four calendar periods (1991–1995, 1996–2000, 2001–2005, and 2006–2010). Patients older than 65 years accounted for almost one in five auto-SCTs in the most recent calendar period. This group of patients also registered the greatest proportional increase in auto-SCT activity. OS improved more in older than in younger patients. Two-year estimates of OS were 83% in patients aged 65–69 years transplanted between 2006 and 2010, compared to 72% of those transplanted between 1996 and 2000. The two-year OS of patients aged 65–89 years who were transplanted between 1991 and 1995 was only 55%. Day-100 all-cause mortality in patients aged 65–69 decreased from 8% in 1991–1995 to 2.1% in 2006–2010.[39] Multivariate analysis of factors associated with survival is summarized in Table 1. The CIBMTR reported results of 11 430 auto-SCT procedures performed between 2008 and 2011. The cohort was divided into three groups: 18–59 years old ($n = 5818$), 60–69 years old ($n = 4666$), and more than 69 years old ($n = 946$). After a median follow-up of 3 years, median OS was not reached for any cohort. Three-year OS ranged between 72% and 78% in the different age groups. NRM at 1 year was 0% for patients aged ≥70 years, and 2% for the other age groups. Neither 3-year relapse rate nor 3-year PFS were significantly different between groups. The authors concluded that MM patients with adequate performance status or comorbidity assessment should not be excluded from auto-SCT on the basis of age alone.[40] In summary, one-third of all myeloma patients are aged 65–75 years at diagnosis and are candidates for auto-SCT. Based on the studies discussed above, a substantial proportion of those patients may benefit from high-dose MEL followed by auto-SCT. However, a considerable proportion of patients will not be fit enough for full-dose MEL. In this subgroup, MEL 100 auto-SCT may be an option. New well-designed studies investigating the role of auto-SCT for elderly MM patients are needed. These studies should include induction therapies and maintenance based on novel agents. It will also be important to establish evidence-based methods for patient selection, which consider chronological age together with objective comorbidity or frailty scores.[41]

Table 1. Factors associated with survival after auto-SCT: a proportional hazards regression analysis by the EBMT.[39] The relative risk of death increased progressively for every age interval when compared with patients younger than 40 years.

	n	RR	95% CI	*p* value
Age at auto-SCT				
<40	1594	1.00	–	–
40–49	8082	1.22	1.09–1.35	<0.001
50–59	20 439	1.39	1.25–1.54	<0.001
60–64	12 259	1.51	1.36–1.68	<0.001
65–69	6680	1.78	1.60–1.99	<0.001
≥70	1258	2.09	1.82–2.40	<0.001
Calendar period				
1991–1995	2398	1.00	–	–
1996–2000	8339	0.78	0.73–0.83	<0.001
2001–2005	16 248	0.64	0.60–0.68	<0.001
2006–2010	23 327	0.57	0.53–0.61	<0.001
Disease status at auto-SCT				
>PR	9831	1.00	–	–
PR	33 144	1.13	1.077–1.187	<0.001
<PR	7337	1.58	1.492–1.675	<0.001
Gender				
Male	29 347	1.00	–	–
Female	20 965	0.92	0.921–0.891	<0.001
Disease duration before auto-SCT				
<12 months	37 614	1.00	–	–
≥12 months	12 698	1.07	1.068–1.029	<0.001

Auto-SCT, autologous stem cell transplantation; CI, confidence interval; RR, relative risk.

Allo-SCT is not commonly performed in newly diagnosed patients, but its use in later phases has been increasing somewhat in the EBMT community. However, most patients often undergo an allo-SCT when the disease is likely to be too advanced to be sensitive to *graft-versus-myeloma* effect of donor T cells. Sizable studies that compared the safety and efficacy of auto-SCT versus allo-SCT in newly diagnosed MM patients predated the clinical use of new drugs, and their clinical outcomes were controversial.[6,7,42,43] Two meta-analyses showed higher response rates after allo-SCT that were, however, offset by a higher NRM that did not eventually translate into an advantage in OS.[15,44] Of note, in most studies the follow-up was rather short; a new individual patient meta-analysis on the same studies with much longer follow-up will be carried out soon (Costa et al. personal communication). The lack of definitive studies that assess the combination of allo-SCT with new drugs prevents defining the current role for allo-SCT. Of note, recent findings on the evaluation of molecular remission (MR) after allo-SCT (see also next paragraph) showed, however, high response rates even in high-risk patients. Kröger et al. investigated the impact of MR and high-risk cytogenetics, defined as the presence of del(17p13) and/or t(4;14) by FISH analysis, after tandem auto/allo-SCT with an MEL and fludarabine-based RIC allo-SCT.[45] The achievement of MR resulted in long-term disease control. The 5-year PFS was 17% for clinical PR, 41% for clinical complete remission (CR), 57% for MR, and 85% for sustained MR. Importantly, there was no statistically significant difference in clinical outcomes between patients with del(17p13)/t(4;14) and those without. The authors concluded that a tandem auto/allo-SCT may overcome the negative prognostic effect of del(17p13) and/or t(4;14). More recently, Ladetto et al. evaluated minimal residual disease (MRD) by qualitative nested-polymerase chain reaction (PCR) and quantitative PCR (qPCR) in patients treated with tandem auto-SCT followed by a non-myeloablative allo-SCT. Patients did not receive consolidation/maintenance with donor lymphocyte infusions (DLI) and/or new drugs. After a median follow-up of 12.1 years from diagnosis, the rate of negativity by nested-PCR increased up to 47% at 12 months after allo-SCT. qPCR revealed a decrease in tumor burden of 13.80 ln from baseline over the course of treatment ($p < 0.001$). The overall MR rate was 63% at

2 years by qPCR. Median OS and EFS were not reached in patients who attained nested-PCR negativity while they were 3.3 and 1.5 years, respectively, in the remaining patients ($p = 0.023$ and $p = 0.009$). One strength of this study was the very long median follow-up, which may suggest that disease eradication had been achieved in a subset of patients.[46]

Overall, new drugs have made allo-SCT a less attractive treatment because of its toxicity. However, the mechanisms of actions of new drugs and the *graft-versus-myeloma* effects are not mutually exclusive. Kröger et al. showed that the addition of IMiDs or proteasome inhibitors to DLI could increase the CR rate. Thirty-two patients were treated with DLI plus either an IMiDs or bortezomib. Nineteen patients achieved CR, of which 17 had no evidence of disease by multiparameter flow cytometry (MFC) and 15 by molecular analysis.[45] Thus, continuous exploration of post SCT therapies with either IMiDs or proteasome inhibitors may show a superiority of allo-SCT as salvage therapy. Some phase II trials evaluating these concepts have been performed.[45,47–52] Further evidence of a synergism between new drugs and donor T cells has recently been shown in a comparative study in newly diagnosed patients, where higher response rates to salvage therapies with new drugs were observed in the allo-SCT patients. This translated into significantly longer OS from relapse after the allo-SCT, compared to a second auto-SCT [Figure 2].[53] Overall, the combination of 'new drugs' with *graft-versus-myeloma* has not yet been explored in well-designed prospective studies though their efficacy in relapsed patients after an allo-SCT has been reported in several studies.[39] The feasibility of bortezomib within a RIC, and as maintenance post-allo-SCT was investigated in a small phase II trial.[51] Conditioning consisted of fludarabine, MEL, bortezomib while maintenance treatment consisted of cycles of iv bortezomib. Sixteen high-risk patients relapsing after auto-SCT were prospectively enrolled. Nine/16 (56%) and 5/16 (31%) achieved CR and PR respectively. In this heavily pre-treated population, the 3-year cumulative incidence of NRM, relapse and OS were 25%, 54%, and 41% respectively. For the first time, this study showed safety and efficacy of an intensified conditioning with a new drug in high-risk patients. The concept of maintenance treatment after allo-SCT was also introduced. These findings allowed the design of a prospective multi-center trial through the EMN. The trial aims at optimizing clinical outcomes by reducing relapse risk and incidence ofgraft-vs.-host disease (GVHD) with the integration of bortezomib and lenalidomide in the treatment plan. Candidates are high-risk patients, younger than 70 years, with early relapse after first-line treatment. Preliminary data will soon be available (Perez-Simon, personal communication).

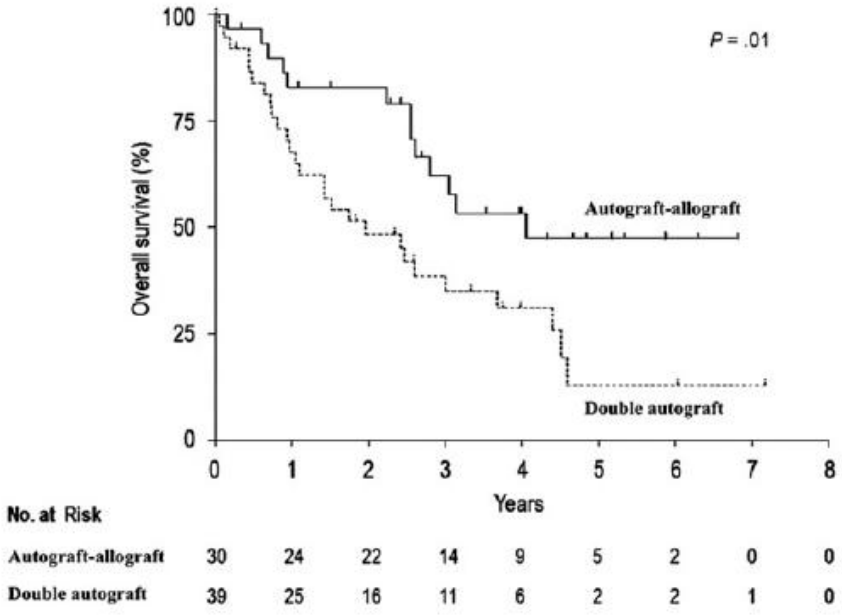

Figure 2. Relapsed patients after non-myeloablative allo-SCT (solid line) and second high-dose melphalan auto-SCT (dotted line). Overall survival from relapse and start of salvage therapy with new drugs.[53] (Figure adapted from Giaccone et al.).

In summary, the real role of allo-SCT remains to be determined. However, it may be ethical to evaluate the unexplored combination of *graft-versus-myeloma* effect along with novel agents in young high-risk and/or early relapsed patients, where life expectancy is poor even in the era of new drugs.

Role of minimal residual disease

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In the past decades, increased success in MM treatment has boosted interest in MRD detection as an effective option to measure response and identify patients at higher risk of relapse. Three approaches are currently available and include allele-specific oligonucleotide PCR (ASO-PCR) and its most recent derivatives digital droplet PCR, MFC, and next-generation sequencing (NGS).[54–59] Characteristics of the three methods are compared in Table 2. Potential advantages of the recent introduction of NGS include a higher rate of target identification, non-reliance on patient-specific primers, possibility of performing sub-clone analyses, and possibly improved sensitivity.[56,57,60] However, it has not yet been standardized and compared with standard PCR-based MRD methods. Moreover, its clinical validation is still in progress. A recent comparison between qPCR and NGS showed highly concordant results ($p < 0.001$, $R = 0.791$).[46] Martinez Lopez et al. also reported high clonotype identification and significant predictive value for MRD assessment by NGS in 110 patients with MM. In the setting of SCT, the first evidence for the impact of different treatments on MRD dates back to the end of the last century. Older studies emphasized the lack of consistent MR achievement after auto-SCT as opposed to allo-SCT. In fact, a maximal cytoreduction in approximately 50% of the patients was reported after allo-SCT.[61,62] Subsequent studies showed the predictive value of a major reduction of tumor burden assessed either by MFC or by molecular methods.[63,64] Moreover, Paiva et al. showed that MRD assessment could easily be combined with baseline cytogenetics to predict clinical outcomes.[55] The introduction of novel agents represented a major step forward in the treatment of MM. MRD studies by molecular methods after auto-SCT and consolidation with VTD showed profound cytoreduction and frequent MR.[65] After a median follow-up of 8 years, OS was 72% in patients who reached MRD-negativity compared with 48% in those with MRD persistence ($p = 0.041$). Moreover, the reappearance of MRD-positivity after a period of MR was associated with an increased risk of relapse with a median time between molecular and clinical relapse of 11 months.[54] Finally, the same group reported more recent results on the impact of non-myeloablative allo-

SCT on MRD. The tandem approach auto-SCT followed by a non-myeloablative allo-SCT in newly diagnosed MM-induced MR (nested-PCR) in approximately 50% of patients at 12 months from SCT. Overall, the MR rate was 63% at 2 years by qPCR. At a remarkable median follow-up of 12.1 years, median OS and EFS were not reached in patients who had achieved nested-PCR negativity.[46] *Graft-versus-myeloma* after non-myeloablative allo-SCT produced rates of prolonged MR similar to those after myeloablative allo-SCT and higher than those obtained after auto-SCT and consolidation with new drugs.

Table 2. Comparison of three methods for the detection of minimal residual disease.

	Flow cytometry	ASO-PCR	NGS
Sensitivity	Limited by the technical applicability of antibodies. Sensitivity for a four-color assay $>10^{-4}$. Higher sensitivity with 8 or 10 colors and new bioinformatic tools.	Limited by cell number and sometimes background. Sensitivity $>10^{-5}$	Limited by cell number. Sensitivity $>10^{-6}$ Very low intrinsic background.
Intra-clone variability	Clones expressing aberrant phenotypes can emerge.	Hypersomatic mutations can affect target identification and assay sensitivity.	Possible subclone identification in mature lymphoid malignancies. Bioinformatic algorithms needed.
Effort required	Fast results, experienced operators needed.	5–7 working days for assay establishment needed.	Dependent on HTS device. Bioinformatic expertise is crucial.
Standardization	Ongoing process. EuroFlow consortium.	Achieved for NHL within EuroMRD consortium. Easily adaptable to MM.	EuroCLONALITY-NGS consortium. EuroMRD consortium.

ASO-PCR, allele-specific polymerase chain reaction; NGS, new generation sequencing; MRD, minimum residual disease; NHL, non-Hodgkin's lymphoma; HTS, high throughput sequencing.

Taken together, all these findings show that: a) MRD, evaluated either by MFC, qPCR or, more recently, by NGS, is a major predictive factor for survival in MM; b) treatments should aim at maximal cytoreduction and MRD negativity to achieve 'functional cure'; c) MRD-guided treatment of molecular persistence and/or molecular relapse may represent attractive future modalities in the context of large prospective trials.

Stem cell transplantation in amyloidosis

Jump to section

Light-chain amyloidosis (AL) is a rare plasma cell disorder that differs from MM in terms of tumor biology and clinical behavior. Treatment strategies for AL and MM are somewhat similar. Recently, the introduction of new drugs in the treatment algorithm together with the use of high-dose MEL and auto-SCT significantly

improved clinical outcomes. AL amyloidosis accounts for about 120 SCT per year in Europe. Cardiac and renal damage are common findings that contribute to reducing the number of auto-SCT candidates.[66] Dispenzieri et al. reported the Mayo Clinic experience with auto-SCT in AL and MM. Among 2245 patients diagnosed with AL between 1996 and 2011, 454 (20.2%) underwent auto-SCT. In the same study period, 1116 MM patients received an auto-SCT. The conditioning was high-dose MEL for the vast majority. AL patients showed a higher day-100 NRM (8.8% versus 1.4%, $p < 0.0001$). However, median OS for AL and MM groups were 113.3 and 59.5 months, respectively ($p < 0.0001$). AL patients who achieved CR after auto-SCT (40.1% of treated AL patients) had a surprisingly high 5-year estimate of OS (90.5%).[67] Long-term results on another large series of 421 AL patients are available. All patients received high-dose MEL and auto-SCT. By intention-to-treat analysis, the CR rate was 34%. Median OS in CR patients was 13.2 years. Consistent with previous observations, OS was significantly longer in patients in CR compared to patients with measurable disease after auto-SCT. However, the authors reported a high organ response rate even in patients who did not achieve CR.[68] Auto-SCT markedly improved clinical outcomes of AL patients. Unfortunately, only a minority was eligible for the procedure. The proportion of auto-SCT candidates may be increased by optimizing early diagnosis and induction therapy, and by identifying NRM predictors.

Reports on allo-SCT in AL are anecdotic. The largest retrospective study was performed by the EBMT in 2006. Seven patients received myeloablative and eight received RIC conditioning regimens. Long-term survival was observed in seven patients. The overall NRM was 40%.[69] The university of Hamburg and Heidelberg reported the efficacy of DLI in two patients.[70] Allo-SCT may be a reasonable option for medically fit patients who do not achieve a remission or relapse after auto-SCT.

Stem cell transplantation in polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes

Jump to section

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes syndrome may be another indication for high-dose MEL and auto-SCT in selected patients though published data are limited.[71]

Future directions: immunotherapy

Jump to section

Novel strategies aimed at obtaining specific immune responses against MM cells are under development. Phase I or II clinical trials on safety and efficacy of monoclonal antibodies, bispecific T-cell engaging molecules (BiTEs), or chimeric antigen receptor (CAR) T-cells are currently in progress. Monoclonal antibodies, when engineered into BiTEs, can drive CD8 T-cells against tumor cells and give rise to a specific cytotoxic activity.[59,60] Moreover, antibodies directed against the programed death receptor-1 (PD1)/PD ligand-1 (PD-L1) pathway are under investigation.[72] PDL1 blockade led to MM eradication in murine models, and a phase II trial of anti-PD1 after auto-SCT in MM is currently recruiting participants (NCT02331368). Preclinical data raised concerns on increased GvHD after PD-L1 blockade in allo-SCT recipients.[73]

CARs are synthetic proteins with an antigen recognition portion and an intracellular activation domain [Figure 3]. They allow T-cells or NK-cells to direct their cytotoxic potential activity against specific targets. CAR cells may display antibodies specific for MM surface antigens such as kappa light chains (NCT00881920), CD138 (NCT01886976), Lewis Y antigen (NCT01716364), B-cell maturation antigen, or CS1.[74] Very encouraging results have recently been published with NY-ESO-1-specific TCR-engineered T cells.[75,76] Other possible effectors to harbor CAR constructs are Vγ9Vδ2 T cells. They have spontaneous anti-tumor activity and are involved in immunosurveillance processes.[77] Despite a number of possible targets in MM, the clinical efficacy of CAR cells has been shown only in patients with CD19 + hematological malignancies such as chronic and acute lymphoid leukemias.[78–80] Serious side effects have been reported. Toxicity is primarily caused by cross-reactions of CAR cells with host tissues that lead to tumor lysis syndrome, cytokine storm syndrome or induction of GvHD in the setting of allo-SCT. In murine models, the co-expression of a suicide gene allowed rapid pharmacological ablation of CAR cells, decreasing side effects without impairing efficacy.[81]

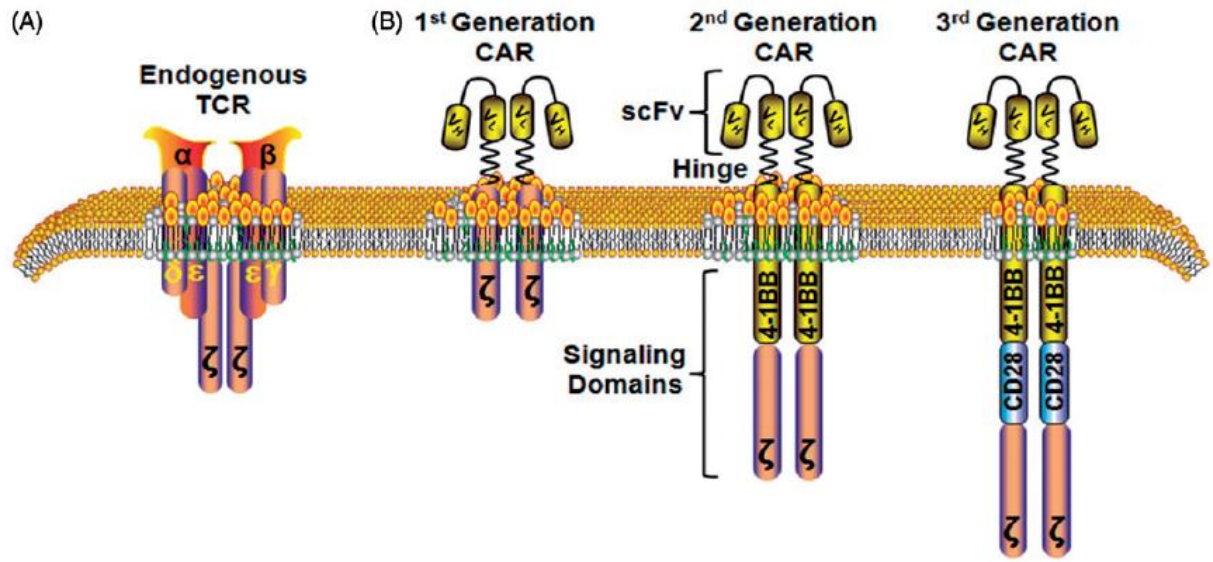

Figure 3. T cells can be redirected to tumor-specific antigens. (A) T cells with a single endogenous T-cell receptor (TCR). (B) Alternatively, T cells can be engineered to express chimeric antigen receptors (CARs) that recognize surface antigens in an MHC-unrestricted immune-reaction. CAR T cells are composed of an extracellular portion, a hinge region, and an intracellular signaling domain. The second generation CAR T cells possess a co-stimulatory domain (e.g. 4-1BB or CD28). The third generation CAR T cells have two co-stimulatory intracellular domains.[74] (Figure adapted from Garfall et al.).

Finally, another interesting field is tumor-specific vaccination. Vaccines may generate MM-specific immunity that selectively targets malignant cells while minimizing toxicity to other tissues. Investigators are evaluating the role of various immunogenic targets such as Wilms Tumor 1 gene products, cancer testis antigens, hyaluronic acid-mediated motility receptor receptor for hyaluronan mediated motility (RHAMM), Dickkopf-1, NY-ESO: New York esophageal squamous cell cancer antigen, melanoma associated antigen-C1 (MAGE-C1) or plasma cell antigens such as CD138 or MUC1. Clinical data are currently limited.[82] Results of ongoing trials will help clinicians to better define safety and efficacy of MM antigen vaccines.

Conclusion

Jump to section

The treatment paradigm in MM is rapidly changing. It is now widely assumed that induction therapy should include novel agents, especially proteasome inhibitors and/or IMiD. Bortezomib-based or lenalidomide-based combination therapies provide deep responses. Encouraging data on the newer proteasome inhibitor carfilzomib in newly diagnosed patients are now available. The drug seems to be less toxic with less peripheral neuropathy compared to bortezomib.[83] Despite the wide armamentarium of new drugs, auto-SCT is still considered the standard of care in young MM patients. Peripheral hematopoietic cell harvests are commonly adequate in the vast majority of patients also due to the availability of plerixafor for predicted poor mobilizers. Risk stratification has been shown to predict prognosis, but it has not yet been used for individualizing therapies. While the upfront treatment plan uniformly includes induction with new drugs and a first auto-SCT in fit patients, whether and when to consolidate responses with a second auto-SCT remains a matter of debate. Owing to the lack of conclusive studies, policies greatly vary from institution to institution. One may consider a second auto-SCT as salvage at relapse or in selected patients who do not achieve good responses after the first auto-SCT. The role of IMiDs is a matter of debate in the maintenance phase following consolidation post auto-SCT. The quality of life is an important issue to address in future clinical trials. More evidence is needed to determine optimal dosing, scheduling, and duration of therapy with novel agents, as they may strongly affect the quality of life.
Despite the dramatic improvement in OS after the introduction of new drugs, relapse eventually occurs. This contributed to allo-SCT being used as consolidation or salvage treatment. Allo-SCT is the only treatment able to eradicate the disease. However, data from prospective comparisons between auto-SCT and low-intensity allo-SCT from various institutions are not consistent. This pitfall has reduced the use of the allo-SCT procedure, which is now performed in only a small percentage of patients. Allo-SCT may have a role in young patients with high-risk features such as del [13], t(4;14), del(17p), and t(14;16).[84] However, it should not be performed outside of clinical trials.

Finally, innovative immune therapies are under development. CAR cells, vaccines directed against tumor antigens, and monoclonal antibodies (including BiTEs) have shown promising results in the preclinical setting and in small patient series. Those new treatments have the potential to overcome drug resistance in MM. Furthermore, immune-therapies may synergize with novel agents and increase the depth and length of remissions, becoming a new option for MM patients.

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